Summary of Patients Screened/Enrolled

Pt	Age	Sex	Comorbidity	Disease length	Previous Treatments	Concomitant Treatments	Enrolled?
01	62	M	MGUS	2yrs	Cyclosporine, gevokizumab, prednisone, RA-18C3	ASA, atorvastatin, carvedilol, cilostazol, clopidogrel, mupirocin, omeprazole, oxycodone, prednisone, spironolactone, triamcinolone, Bactrim DS.	Yes
02	23	M	Bruton's agammaglo-bulinemia	2yrs	Prednisone, gevokizumab	Ibuprofen, vancomycin, Zosyn, morphine, Levaquin, Motrin, Benadryl, ampicillin, APAP, prednisone, Hizentra, Claritin D, Asmanex, tramadol, Paxil, omeprazole	Yes
03	55	F	+ASO, minor MGUS	20yrs	Debridement, prednisone, vein ablation	Tramadol, Zosyn, dilaudid, vancomycin, cefepime, KCl, Hylenex, gadoterate meglumine, minocycline, senokot, naproxen, morphine, metronidazole, heparin, Ca-VitD, docusate, pentoxifylline, maxipime, APAP, doxycycline, prednisone	Yes
04	49	F	IgA vasculitis	3yrs	Debridement, dapsone, MMF, fluocinonide, silver-sulfadiazene		No
05	58	M	Presumptive Crohns (based on Prometheus testing)	50yrs	Skin grafting, hyperbaric tx, debridement, collagen/silver dressings, mafenide cream	Lipitor, dexamethasone, Benadryl, Allegra, Lopid, Norco, Combivent, Syntroid, multiVit, probiotic, Januvia, Cozaar, mafenide, Metformin, Actos, Dakins soln, APAP, Immodium, Flonase, lidocaine 1% inj, fluconazole, meropenem, docusate-senna, GoLytley, daptomycin, vancomycin, Alteplase, metronidazole, MgSO4, heparin, Lispro, gadoterate meglumine, dilaudid,	Yes

1.1 PRIMARY ENDPOINTS

The proportion of subjects achieving a two point reduction in the five-point investigator global assessment (IGA) for the target ulcer from baseline to week 12.

Pt	Baseline IGA	Completion IGA	Notes (or completion wk)
01	3	3	
02	3	N/A (not captured at Wk 2)	Lost to FU after Wk 2
03	3	4	EOT visit at Week 6
05	4	4	EOT visit at Week 6
Mean	3.25	3.67	

1.2 SECONDARY ENDPOINTS

-Frequency of total closure of target and total ulcers from baseline to week 12

Pt	Closure of Target?	Closure of Any?	Notes (or completion wk)
01	No	No	
02	No	No	Lost to FU after Wk 2
03	No	No	ET visit at Week 6
05	No	No	ET visit at Week 6
Mean	No	No	

-Change in total surface area of target/total ulcers from baseline to week 12

Pt	Baseline Area	Completion Area	Notes (or completion wk)
01	14.56 cm^2	19.38 cm^2	
02	2.28 cm^2	3.96 cm^2	Lost to FU after Wk 2
03	23.4 cm^2	41.4 cm^2	ET visit at Week 6
05	20.48 cm^2	32 cm^2	ET visit at Week 6
Mean	15.18 cm^2	24.19 cm^2	

-Change Patient Global Assessment (PGA) from baseline until week 12

Pt	Baseline PGA	Completion PGA	Notes (or completion wk)
01	3	3	
02	3	N/A (not captured at Wk 2)	Lost to FU after Wk 2
03	8	7	ET visit at Week 6
05	10	6	ET visit at Week 6
Mean		5.33	

-Change in patient pain perception using 10-point visual analog scale from baseline to week 12

Pt	Baseline Pain VAS	Completion Pain VAS	Notes (or completion wk)
01	6	6	
02	5	N/A (not captured at Wk 2)	Lost to FU after Wk 2
03	10	8	ET visit at Week 6
05	4.5	4	ET visit at Week 6
Mean	6.37	6	

-Change in patient quality of life using the dermatology life quality index (DLQI) from baseline to week 12

Pt	Baseline DLQI	Completion DLQI	Notes (or completion wk)
01	6	7	
02	3	3	Lost to FU after Wk 2
03	15	17	ET visit at Week 6

05	18	6	ET visit at Week 6
Mean	10.5	5.75	

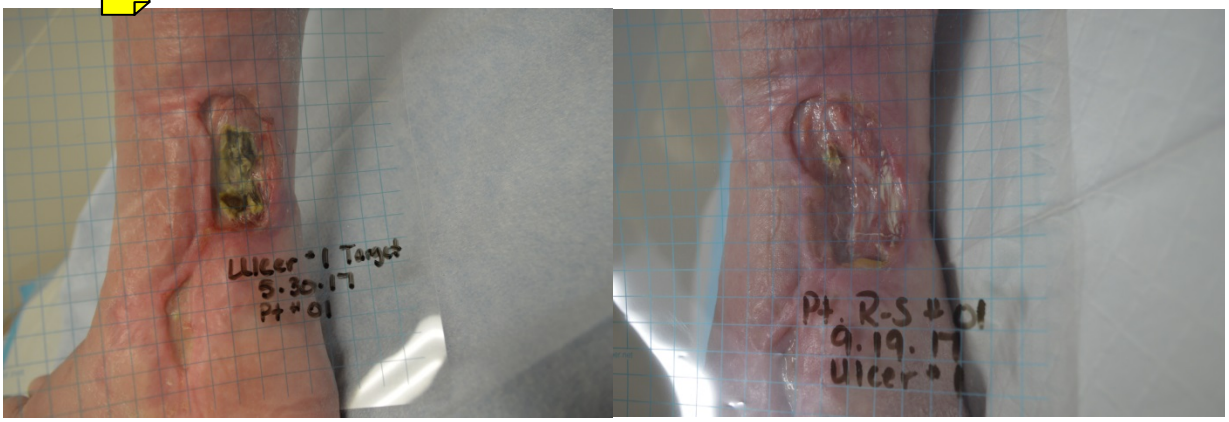
1.3 EXPLORATORY ENDPOINT

-Evaluation of an [IGA x Ulcer Area] scoring metric for target ulcer at each time-point
-Change in microbiome of ulcer between baseline and week 12
-Change in inflammatory markers between baseline and week 12 – C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), absolute neutrophils, total leukocytes, IL-1, IL-6, IL-8, and TNF in serum.
-Change in serum biomarker (if can be ascertained), depending on underlying cause (i.e. perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and anti-saccharomyces cerevisiae antibodies (ASCA) in patients with IBD, anti-streptolysin-O (ASO) in patients with streptococcus- driven disease, or levels of monoclonal/polyclonal protein in patients with MGUS/elevated IgA levels.

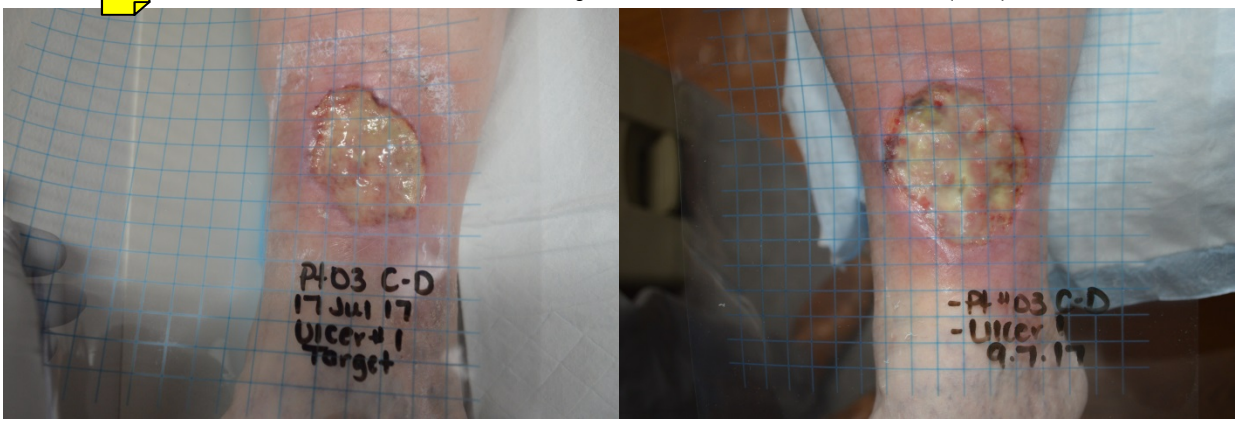
Due to few patients and only one patient completing a full 12 weeks of the study, the exploratory endpoints were not further assessed and rather nanostring technology was performed to evaluate whether there were gene expression markers of the biopsy pre-post treatment in the skin demonstrating diminished inflammatory pathways. Data attached. Unfortunately, there were very few genes showing consistent changes in regulation and of those, the change in expression was small.

Clinical Image and Timeline:
(Note: As Subject 02 only completed visit 2, there are no photographs to compare to baseline)

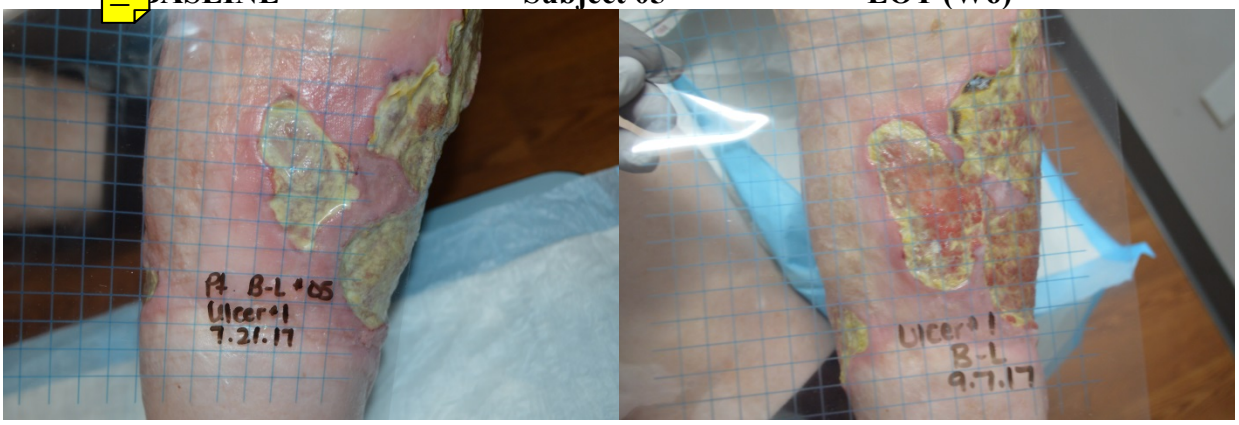
BASLINE **Subject 01** **EOT (W16)**



BASLINE **Subject 03** **EOT (W6)**



BASLINE **Subject 05** **EOT (W6)**



ANALYSIS AND PUBLICATION PLAN:

The goal of the study will be a publication in a high-impact international dermatology journal such as the *Journal of the American Academy of Dermatology*, *JAMA Dermatology* or *British Journal of Dermatology*. We aim for a national level presentation at the American Academy of Dermatology annual meeting.

Sample Size: 5

Proposed Enrollment and Study Completion Plan:

Total number of patients to be enrolled	5
Number of investigative sites	1
Total study length	16 weeks
Enrollment period	Up to 6 weeks
Treatment period	12 weeks
Anticipated date of first patient visit	3/1/17
Anticipated date of the last patient visit	3/1/18
Anticipated date of final study report submission to Lilly	5/31/18
Anticipated publication date	12/31/2018

Study Synopsis:

STUDY SYNOPSIS

Title:	**An Open-Label, Proof-Of-Concept, Study of Ixekizumab in the Treatment of Pyoderma Gangrenosum**
Protocol number:	
Phase:	II
Indication:	Pyoderma Gangrenosum
Study drug and comparator:	Ixekizumab SQ No comparator is used in this study.
Main Objectives:	**Primary Objective**: the proportion of subjects achieving a two point reduction in the five-point investigator global assessment (IGA) for the target ulcer from baseline to week 12 **Secondary Objectives**: -Analysis of frequency of total closure of target and total ulcers from baseline to week 12 -Analysis of change in total surface area of target/total ulcers from baseline to week 12 -Analysis of change Patient Global Assessment (PGA) from baseline until week 12 -Analysis of change in patient pain perception using 10-point visual analog scale from baseline to week 12 -Analysis of change in patient quality of life using the dermatology life quality index (DLQI) from baseline to week 12
Study design:	This is a Phase II study that will be open label and enroll a total of five patients. These patients will have histological testing to rule out competing etiologies and require 3rd

	party adjudication/confirmation on agreement of the diagnosis. These patients will undergo 12 weeks of ixekizumab dosed every 2 weeks with follow-up until week 16.
Major inclusion/exclusion criteria:	For the complete list of inclusion/exclusion, criteria refer to Section 4. <u>Major inclusion criteria:</u> - Have a clinical diagnosis of classic PG for at least 3 months as determined by the investigator and an external reviewer on the basis of results from clinical, histological and laboratory assessments - At screening, have a PG ulcer characterized by 'item a' AND 3/5 features in 'item b' OR 2/5 features in 'item b' with support from one of the conditions listed in c. a. Stable or increasing size within 2 months preceding screening by patient report or documentation b. Features such as violaceous border, undermining, cribriform scarring, pustules, peristomal location c. Identifiable secondary systemic condition, such as IBD, arthritis, MGUS, noncancerous hematologic disease, streptococcal carriage, levamisole-tainted cocaine, Bruton's agammaglobulinemia - Have a PG target ulcer that has an area ≥ 2 cm^2 and ≤ 200 cm^2 at screening - Initial IGA of 3 or higher on a 5 point scale (0-4) <u>Major exclusion criteria:</u> 1. Any condition (e.g., psychiatric illness, severe alcoholism, or drug abuse) or situation that may compromise the ability of the subject to give written informed consent, may put the subject at significant risk, may jeopardize the subject's safety after exposure to the study drug, may confound the study results, or may interfere significantly with the subject's participation in the study 2. History of malignancy within 2 years of screening other than carcinoma in situ of the cervix or adequately treated, non-metastatic, squamous or basal cell carcinoma of the skin 3. History of seropositivity for HIV antibody; active or carrier status of hepatitis B [surface antigen (HBsAg) positive, or core antibody (anti-HBc) positive with negative surface antibody]; active hepatitis C (i.e. not treated or not cleared spontaneously, as confirmed by HCV PCR) 4. History of severe allergic or anaphylactic reaction to

	monoclonal antibodies 5. Systemic infection (excluding wound colonization) requiring oral antibiotics within 2 weeks of Day 0 6. History of the following treatments: a. Anti-TNF or other biologic therapies within 5 half-lives of screening b. Changes (addition, discontinuation, or changes in dose) in immunosuppressive medication (including cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, apremilast, dapsone, or corticosteroids within 2 months of Day 0 c. Systemic corticosteroids > 20 mg per day (prednisone or prednisone equivalent) within 8 weeks of Day 0, or change in dose within 8 weeks of Day 0. Steroids may be tapered (although not increased above the Day 0 dose) during the trial as determined by the investigator. d. Intralesional corticosteroids within 8 weeks of day 0; topical immunomodulators are permitted. e. Wound debridement within 2 weeks of Day 0; dressing changes allowed per investigator discretion. g. Systemic antibiotics within 2 weeks of Day 0 h. Live, attenuated vaccines within 3 months of Day 0; or live, seasonal-flu- or H1N1 vaccines within 2 weeks of Day 0. Note: recombinant- and/or killed vaccines are permitted. i. Hyperbaric treatment within 4 weeks of Day 0 j. Investigational drug or investigational device within 30 days or 5 half-lives of Day 0, whichever is longer k. Prior exposure to ixekizumab l. Other treatments not described above should be maintained at a stable dose and frequency throughout the study as best as possible 13. Major, general surgery within 3 months of screening, or anticipated general surgery during the study period 14. Pregnancy, plans to become pregnant during the course of the study, delivery within 3 months of screening, or breast-feeding 15. If previous use of cyclosporine or systemic corticosteroids, failure to have any stabilization/response is exclusionary. This potentially indicates the disease is not PG.
Endpoints:	• Change in IGA between baseline and week 12
Safety plan:	Enrollment and toxicities on this trial will be monitored by

	the principal investigator and the OSU Data and Safety Monitoring Committee (DSMC)
Study treatment:	Ixekizumab subcutaneous injection 160 mg at d0, 80 mg q 2 weeks with the last dose at week 12.
Concomitant therapy and clinical practice:	As PG is a disease responsive to immunosuppression, use of concomitant medications will be carefully monitored, and patents will be required to have stable or worsening disease on a consistent dose of immunosuppression at screening. 1. Mycophenolate mofetil, azathioprine, cyclosporine, leflunomide, dapsone, apremilast and methotrexate will be allowed, but the patient is required to have stable/worsening disease for 4 weeks prior to screening, while on a stable dose of immunosuppression for > 8 weeks prior to baseline. 2. Anti-TNF or other biologic therapies will not be allowed within 5 half-lives before screening, or during the study. 3. Oral corticosteroids above 20 mg daily of prednisone (or equivalent) are excluded. Lower doses are allowed provided they are prescribed at stable doses for two months prior to baseline and are 20 mg or less per day of prednisone or other equivalently-dosed corticosteroids. 4. Intralesional corticosteroids within 4 weeks of screening and during the study are not permitted 5. Other therapies that are non-immunosuppressive and non-investigational can be started or continued at physician discretion provided the medicine has no history of association with progressive multifocal leukencephalopathy. Antibiotics may be used as needed for evidence of superinfection, positive culture results, malodor, green discharge, etc.
Statistical methods:	The primary objective of a two-point IGA decrease in the target ulcer will be analyzed as the difference from baseline, with the null hypothesis that no patients will obtain the specified improvement if the investigational product does not have efficacy. The endpoint will be analyzed using the Fisher Exact test. The secondary and exploratory objectives will be analyzed in comparison to baseline measurements and at each time point to evaluate for efficacy using either the Fisher Exact test/Chi-square test or the Wilcoxon Rank Sums test. We anticipate that the basic statistics will be completed within 1-2 months of the last patient completing his/her week 12 visit. Analyzing the interferon multiplex assay and microbiome will take longer, but will primarily be descriptive at the different time points and be analyzed by T-testing for continuous variables